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## **Integrating first-line treatment options into clinical practice: what's new in advanced melanoma?**

Dummer, Reinhard ; Schadendorf, Dirk ; Ascierto, Paolo A ; Larkin, James ; Lebbé, Celeste ; Hauschild, Axel

**Abstract:** Melanoma remains a serious form of skin cancer in Europe and worldwide. Localized, early-stage melanomas can usually be treated with surgical excision. However, the prognosis is poorer for patients with advanced disease. Before 2011, treatment for advanced melanoma included palliative surgery and/or radiotherapy, and chemotherapy with or without immunotherapy, such as interleukin-2. As none of these treatments had shown survival benefits in patients with advanced melanoma, European guidelines had recommended that patients be entered into clinical trials. The lack of approved first-line options and varying access to clinical trials meant that European clinicians relied on experimental regimens and chemotherapy-based treatments when no other options were available. Since 2011, ipilimumab, an immuno-oncology therapy, and vemurafenib and dabrafenib, targeted agents that inhibit mutant BRAF, have been approved by the European Medicines Agency for the treatment of advanced melanoma. More recently, the MEK inhibitor, trametinib, received European marketing authorization for use in patients with BRAF mutation-positive advanced melanoma. In 2014, the anti-PD-1 antibody nivolumab was approved as a first-line therapy in Japan. Whereas nivolumab and another anti-PD-1 antibody, pembrolizumab, were approved as second-line therapies in the USA, their recent approval in Europe are for first-line use based on new clinical trial data in this setting. Together these agents are changing clinical practice and making therapeutic decisions more complex. Here, we discuss current and emerging therapeutic options for the first-line treatment of advanced melanoma, and how these therapies can be optimized to provide the best possible outcomes for patients.

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# Integrating first-line treatment options into clinical practice: what's new in advanced melanoma?

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Melanoma remains a serious form of skin cancer in Europe and worldwide. Localized, early-stage melanomas can usually be treated with surgical excision. However, the prognosis is poorer for patients with advanced disease. Before 2011, treatment for advanced melanoma included palliative surgery and/or radiotherapy, and chemotherapy with or without immunotherapy, such as interleukin-2. As none of these treatments had shown survival benefits in patients with advanced melanoma, European guidelines had recommended that patients be entered into clinical trials. The lack of approved first-line options and varying access to clinical trials meant that European clinicians relied on experimental regimens and chemotherapy-based treatments when no other options were available. Since 2011, ipilimumab, an immuno-oncology therapy, and vemurafenib and dabrafenib, targeted agents that inhibit mutant *BRAF*, have been approved by the European Medicines Agency for the treatment of advanced melanoma. More recently, the MEK inhibitor, trametinib, received European marketing authorization for use in patients with *BRAF* mutation-positive advanced melanoma. In 2014, the anti-PD-1 antibody nivolumab was approved as a first-line therapy in Japan. Whereas nivolumab and another anti-PD-1 antibody, pembrolizumab, were approved as second-line

therapies in the USA, their recent approval in Europe are for first-line use based on new clinical trial data in this setting. Together these agents are changing clinical practice and making therapeutic decisions more complex. Here, we discuss current and emerging therapeutic options for the first-line treatment of advanced melanoma, and how these therapies can be optimized to provide the best possible outcomes for patients. *Melanoma Res* 00:000–000  
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## Introduction

In 2012, more than 100 000 people were diagnosed with cutaneous melanoma in Europe and 22 200 people died from the disease, making it the most deadly form of skin cancer [1]. Melanoma is also the second most common type of cancer in individuals aged 15–29 years [2]. Given the high incidence rates among young adults and the large number of deaths, melanoma has the potential to result in many years of lost productivity and life [3]. The prognosis for patients with stage III or IV disease has historically been poor, with a median overall survival (OS) of 6–9 months and a 5-year survival rate of less than 5% [4].

Before 2011, palliative surgery and/or radiotherapy, systemic chemotherapy (typically dacarbazine, fotemustine, or temozolomide), and/or immunotherapy with interleukin-2 (IL-2) were the only therapeutic options for patients with unresectable or metastatic disease [5–8]. As none of the systemic treatment options had a proven

effect on OS, they were considered primarily palliative, and European guidelines recommended that patients be preferentially considered for entry into clinical trials of investigational therapies [5–7,9]. The lack of approved and effective first-line treatment options, together with varying access to clinical trials, meant clinicians across Europe often adopted different approaches to disease management, relying on experimental regimens and selecting chemotherapy-based regimens when no other options were available [10].

Since 2011, however, a number of new agents (ipilimumab, vemurafenib, dabrafenib, trametinib, nivolumab, and pembrolizumab) have been approved by the European Medicines Agency (EMA) for the treatment of patients with advanced melanoma [11–16]. These agents have already changed clinical practice. In 2014, nivolumab and pembrolizumab were approved in the USA as second-line therapies, although studies for first-line use (e.g. CheckMate 066, CheckMate 067, CheckMate 069,

KEYNOTE-006) have led to their recent approval in Europe for first-line treatment of patients with advanced melanoma, regardless of *BRAF* status. With the availability of more therapeutic options, treatment decisions are becoming more complex. Now it is not just a case of making do with what is available, but ensuring that the right treatment is provided to the right patient at the right time. In this review, we consider the treatment options that are now available and provide our opinions on how these different agents should be used to maximize patient outcomes and protect some of the years of life that might previously have been lost.

### Current first-line treatment options for patients with advanced melanoma in Europe

#### Targeted therapy

Around 40–50% of melanomas harbor a *BRAF*-activating mutation, 90% of which are at codon 600 [17]. The most common mutation at codon 600 is a replacement of valine with glutamic acid (V600E), accounting for up to 90% of *BRAF* mutations at this location; however, many other mutations exist [18].

Vemurafenib (Zelboraf; Roche/Genentech, San Francisco, California, USA) and dabrafenib (Tafinlar; GlaxoSmithKline, Research Triangle Park, North Carolina, USA) are selective inhibitors that preferentially bind to mutant *BRAF* proteins. Clinical trials have demonstrated rapid responses in many patients treated with vemurafenib or dabrafenib, providing symptomatic relief, prolonged progression-free survival (PFS), and improved median OS, regardless of the line of treatment [19–24]. In first-line registrational trials, median OS with vemurafenib or dabrafenib was longer than previously observed with chemotherapy [20–22]. In the phase 3 randomized clinical trial, BRIM-3, median OS was 13.6 months with vemurafenib and 9.7 months with dacarbazine in patients with previously untreated *BRAF* V600E-positive metastatic melanoma [20]. In the phase 3 randomized cross-over trial BREAK-3, which allowed treatment beyond progression, median OS was 18.2 months with dabrafenib and 15.6 months with dacarbazine in patients with *BRAF* V600E-positive metastatic melanoma [22]. The efficacy of vemurafenib is being evaluated in the setting of brain metastasis with melanoma in phase 2 trials (NCT01378975; NCT01781026).

Like other targeted therapies, *BRAF* inhibitors are associated with a predictable pattern of adverse events (AEs), including skin toxicities such as rash, hyperkeratosis, cutaneous squamous cell carcinoma, keratoacanthoma, fatigue, and pyrexia, as well as rare events such as uveitis and Stevens–Johnson syndrome [17,25–28]. Both vemurafenib and dabrafenib have been approved by the EMA for the treatment of adult patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma [12,13]. Preclinical data suggest that *BRAF* inhibitors are less effective in melanoma cell lines with rare mutations [29]; however, limited clinical evidence suggests that these agents have activity in V600R patients [30,31]. Further

research on the optimal treatment of non-V600E *BRAF* melanoma patients is required.

When deciding between *BRAF* inhibitors for the treatment of *BRAF* V600 mutation-positive advanced melanoma, vemurafenib and dabrafenib appear to have similar efficacy, and data for each confirm intracranial activity and activity in patients with the V600K mutation [32–35]. Dabrafenib appears to be associated with less skin toxicity than vemurafenib; for example, in phase 3 trials, cutaneous squamous cell carcinomas were reported in 19% of patients treated with vemurafenib compared with 5% of patients receiving dabrafenib; ultraviolet-dependent photosensitivity reactions also appear to be more commonly reported with vemurafenib (41%) compared with dabrafenib (2%) [19–21,36]. By contrast, vemurafenib is associated with a lower incidence of pyrexia and palmar–plantar erythrodysesthesia, which are common AEs with dabrafenib [25,37].

One drawback to targeted therapy in advanced melanoma is that, in most cases, patients will eventually develop drug resistance [38]. Resistance to *BRAF* inhibitors and patient relapse are common, ultimately affecting the potential for long-term survival [39]. While multiple mechanisms of resistance can bypass chronic *BRAF* inhibition, the predominant pattern of resistance involves *BRAF*-independent reactivation of the mitogen-activated protein kinase (MAPK) pathway. However, MAPK pathway-independent mechanisms may also play a potential role [40,41]. Patients typically remain free from progression for a median of 7 months [19, 21], and as resistance is more likely to occur the duration of benefit can be limited.

Besides *BRAF* inhibitors, the MEK inhibitor trametinib (Mekinist; GlaxoSmithKline) has demonstrated activity in patients with *BRAF*-positive metastatic melanoma, and has recently been approved in Europe. Activated *BRAF* phosphorylates and activates MEK proteins (MEK1 and MEK2) and downstream MAPKs, which regulate proliferation and survival of tumor cells [42]. In a randomized phase 3 trial, trametinib improved rates of PFS and OS compared with chemotherapy. The most commonly reported AEs with trametinib were rash, diarrhea, peripheral edema, and papulopustular dermatitis, an on-target reaction pattern of the epidermis. No secondary skin neoplasms were found [42,43].

Ongoing clinical studies suggest that coinhibition of MEK and *BRAF* could potentially attenuate the development of resistance to *BRAF* inhibition. Final results of the phase 3 COMBI-d trial comparing dabrafenib 150 mg plus trametinib 2 mg versus dabrafenib plus placebo in patients with *BRAF* V600E/K-mutant metastatic melanoma have been reported [44]. The combination of dabrafenib plus trametinib versus dabrafenib alone demonstrated a 33% reduction in the risk of progression ( $P < 0.001$ ) and a 29% reduction in the risk of death (median OS, 25.1 vs. 18.7 months;  $P = 0.011$ ). Interim results of the phase 3 MEK115306

demonstrated that the combination reduced risk of progression by 25% and improved response rate compared with dabrafenib alone (67 vs. 51%), although a specified stopping boundary for OS was not crossed [45]. Interim results from the phase 3 COMBI-v trial showed an OS rate at 12 months of 72% with the combination and 65% with vemurafenib. In this case, the prespecified interim stopping boundary was crossed, and the study was stopped [46]. In addition, the phase 3 coBRIM trial of the investigational MEK inhibitor cobimetinib in combination with vemurafenib demonstrated improvement in PFS compared with vemurafenib alone (9.9 vs. 6.2 months, respectively) [47]. Updated results for BRF113220, a phase I/II study of dabrafenib alone versus combined dabrafenib and trametinib in patients with *BRAF* V600 metastatic melanoma, showed 2-year OS rates of 44% with dabrafenib monotherapy and 51% with dabrafenib 150 mg plus trametinib 2 mg [48].

However, the combination appears to have limited efficacy in patients who are already resistant to *BRAF* inhibitors, and the safety profile of the combination appears to differ from the monotherapy [49,50]. Interestingly, MEK-resistant *BRAF*-mutant advanced melanoma still responds to *BRAF* inhibitor therapy, whereas *BRAF* inhibitor-resistant melanoma does not respond to MEK inhibitor therapy [51].

### Immuno-oncology

The therapeutic potential of immunotherapy in melanoma was initially highlighted in studies investigating activation of the immune system with the cytokines interferon- $\alpha$ 2b and IL-2 [52]. In the metastatic setting, high-dose IL-2 was approved following results from phase 1/2 studies reporting response rates of 10–20%, with 4–6% of patients achieving a durable complete remission [52]. However, high-dose IL-2 has not been shown to improve OS [53], is not suitable for patients with poor performance status, and may be associated with the development of depression [52].

Ipilimumab is a monoclonal antibody that harnesses the immune system by blocking cytotoxic T-lymphocyte-associated antigen-4, an immune checkpoint that negatively regulates T-cell activation. Ipilimumab was the first agent to significantly improve survival compared with control in randomized phase 3 trials of patients with advanced melanoma, irrespective of mutation status [54, 55]. In 2011, ipilimumab 3 mg/kg, administered intravenously every 3 weeks for a total of four doses, received European Union approval for the treatment of adult patients with advanced melanoma who had received prior therapy. Although the approved indication in the USA was broader than in Europe (including patients irrespective of whether or not they had received prior therapy) [56], the European indication for ipilimumab was extended in 2013 to include first-line treatment [11]. Moreover, the National Institute for Health and Care Excellence in the UK proposed that treatment

recommendations be extended to include ipilimumab as an option for first-line advanced melanoma [57]. The decision to expand the use of ipilimumab to treatment-naïve patients was based upon multiple data sets, including pooled data from chemotherapy-naïve patients who were treated with ipilimumab 3 mg/kg in one of four clinical trials, as well as data from patients who received commercially available ipilimumab in the USA who were identified for inclusion in two separate observational studies, providing important insights from the real-world setting [11,58–60].

The pooled analysis of chemotherapy-naïve patients was conducted on the basis that chemotherapies were the only agents approved for previously untreated patients with advanced melanoma in Europe that were not restricted by tumor genotype. With a median follow-up of 11.6 months, median OS for the 78 chemotherapy-naïve patients was 13.5 months, and 54, 32, and 24% of patients were alive 1, 2, and 3 years after treatment initiation, respectively [58].

In the two US observational studies (CA184-338 and CA184-332) with at least 12 months' follow-up since starting treatment with ipilimumab 3 mg/kg, median OS was 14.5 months ( $n=273$ ) and 11.5 months ( $n=157$ ), with 1-year survival rates of 59.2 and 46.7%, respectively [59,60]. These populations represent 'real-world' patients, including elderly patients and those with *BRAF*-mutated melanoma, brain metastases, and poor performance status [59,60]. As may be expected with any therapy, exploratory OS analyses of subgroups in CA184-338 showed higher OS for patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 vs. 1 (21.5 vs. 12.8 months), without brain metastases (17.5 vs. 14.5 months, overall), and with a cutaneous primary site (16.8 months) [59].

As ipilimumab targets the immune system rather than directly targeting the tumor, this agent can be associated with immune-related AEs, such as skin toxicity, colitis (characterized by mild-to-moderate, but occasionally also severe diarrhea), hypophysitis, and hepatitis. AEs associated with ipilimumab are generally manageable by trained physicians using established guidelines that emphasize vigilance and prompt intervention, and the safety profile of ipilimumab is consistent among chemotherapy-naïve, treatment-naïve, and pretreated patients [11,61].

Treatment with ipilimumab can provide patients with durable tumor control and long-term survival benefits, and the Society for Immunotherapy of Cancer treatment recommendations include ipilimumab as an option for a range of patients with stage IV melanoma, including those with or without *BRAF* mutations and those with *KIT* mutations [52]. Clinical trial and real-world data suggest that treatment with ipilimumab may result in long-term survival (>2 years) [8,54,59,60,62–66]. Data

from a pooled analysis of 1861 patients who received ipilimumab at different dosing schedules and lines of therapy across 12 prospective or retrospective studies showed 3-year survival rates of 22% and a plateau effect for a number of years, with a follow-up of 10 years [67]. When an additional 2985 patients treated as part of an expanded access program were included, the 3-year survival rate was 21% and the plateau in survival curves was maintained [67]. It is important to note that because of the unique patterns of response observed with ipilimumab, which are related to its immune-mediated mechanism of action, patients with durable stable disease or evidence of initial disease progression may eventually respond and also achieve prolonged survival [68].

Because of a delayed time to response, tumor kinetics should also be taken into consideration when treating with ipilimumab. Multiple controlled studies of immuno-oncology agents have shown a delayed separation in survival curves, suggesting that patients destined to die before the separation (i.e. within the first 3–6 months of treatment) may not benefit from ipilimumab. An exploratory analysis from the phase 3 MDX010-20 trial found enhanced treatment efficacy for patients with pretreated, advanced melanoma if they survived more than 12 weeks from randomization, perhaps because this increased the opportunity for patients to complete and potentially benefit from all four doses of ipilimumab [69].

The first-line use of new immuno-oncology agents has recently become possible, and combination of ipilimumab with these new agents may become an option for advanced melanoma in the near future. Programmed death-1 (PD-1) is an inhibitory receptor expressed by activated T cells that downmodulates effector functions [70]. Nivolumab (Opdivo; Bristol-Myers Squibb, Princeton, New Jersey, USA) and pembrolizumab (Keytruda; Merck, Kenilworth, New Jersey, USA) are monoclonal antibodies that block PD-1 to stimulate antitumor immune responses [15,16]. In 2014, both agents were approved in the USA in patients who progress after treatment on ipilimumab and, if *BRAF* V600 mutation-positive, a *BRAF* inhibitor, and nivolumab was approved in Japan for unresectable melanoma. Additional trials of these agents for first-line use are either ongoing or have recently been completed.

In CheckMate 066, a phase 3 trial in patients with previously untreated metastatic melanoma without a *BRAF* mutation, 1-year OS was 72.9% for nivolumab versus 42.1% with dacarbazine [objective response rates (ORRs) were 40.0 vs. 13.9%, respectively] [71]. KEYNOTE-006, a randomized, phase 3 study comparing pembrolizumab (10 mg/kg every 2 or 3 weeks) with ipilimumab, met its coprimary endpoints of PFS and OS and was stopped early [72]. Approximately two-thirds of enrolled patients had not received prior systemic therapy. Overall, 6-month PFS rates were 47.3, 46.4, and 26.5% for pembrolizumab every 2 or 3 weeks, and ipilimumab, with estimated 1-year survival rates of 74.1, 68.4, and 58.2%,

respectively. Incidence of treatment-related grade 3–5 AEs was lower with pembrolizumab, at either dose, than with ipilimumab, and no new safety concerns were reported [72].

Results from CheckMate 069, a phase 2, randomized trial of nivolumab in combination with ipilimumab versus ipilimumab alone in patients with previously untreated, advanced melanoma have recently been published [73]. ORR and PFS were significantly greater with combination therapy compared with ipilimumab alone. ORR among patients with *BRAF* V600 wild-type tumors (the primary endpoint) was significantly higher in the combination group (61%) than in the ipilimumab monotherapy group (11%;  $P < 0.001$ ). Median PFS was not reached with combination therapy and was 4.4 months with ipilimumab. Similar efficacy results were observed in patients with *BRAF* mutation-positive tumors.

The safety observed in this study was consistent with previous experience with the combination. The proportion of patients with treatment-related grade 3 or 4 AEs was higher in the combination group (54%) than with ipilimumab (24%); however, most patients who experienced such events (with the exception of endocrinopathies) had complete resolution with the use of established safety guidelines. Treatment-related grade 3 or 4 AEs led to discontinuation of treatment in 38% of the combination group and in 13% of the ipilimumab group. The three deaths reported in the combination group were linked to pre-existing conditions [73].

CheckMate 067 was the first phase 3 trial to evaluate the combination of immune checkpoint inhibitors in any tumor type, wherein treatment-naïve patients received either nivolumab in combination with ipilimumab or each as monotherapy [74]. The coprimary endpoint of PFS was reported as patients continued to be followed up for OS at the time of this publication. Nivolumab, either in combination with ipilimumab (11.5 months) or alone (6.9 months), significantly improved PFS versus ipilimumab alone (2.9 months). Investigator-assessed ORR by Response Evaluation Criteria in Solid Tumors v1.1 was also higher in both the combination and nivolumab monotherapy groups versus ipilimumab alone (57.6, 43.7, and 19.0%, respectively;  $P < 0.001$  for both combination and nivolumab versus ipilimumab).

Treatment with the combination resulted in similar PFS among patients with a *BRAF* mutation (11.7 months) and in those with wild-type *BRAF* (11.2 months). Among nivolumab groups, PFS was the same in patients with PD-L1-positive tumors (14.0 months). However, in patients with tumors negative for PD-L1, the combination conferred a numerical PFS improvement compared with nivolumab alone (11.2 vs. 5.3 months). In contrast to the PFS results, the combination resulted in a numerically higher ORR compared with nivolumab or ipilimumab alone regardless of PD-L1 status. Among those

with PD-L1-positive tumors, ORR was 72.1% for the combination, 57.5% for nivolumab, and 21.3% for ipilimumab alone. In patients with PD-L1-negative tumors, ORR was 54.8, 41.3, and 17.8%, respectively.

Although grade 3 or 4 AEs were generally higher in the combination group than with nivolumab or ipilimumab alone (55.0, 16.3, 27.3%, respectively), the safety profile of the combination was consistent with earlier experience and no new safety signals were identified, except that more patients had multiple toxicities. Most select (immune-mediated) AEs were managed and resolved with established safety guidelines. There was one treatment-related death in each monotherapy group, but there were none in the combination group [74].

Following a positive opinion from the Committee for Medicinal Products for Human Use, EU approval of nivolumab monotherapy for first-line/second-line treatment of advanced melanoma was announced in June 2015 [75]. On the basis of the demonstrated efficacy and manageable safety profile by trained physicians in clinical trials, the combination of nivolumab and ipilimumab shows promise for the future management of patients with advanced melanoma as a first-line therapy. The need to evaluate patients by PD-L1 status for combination therapy remains to be determined.

### Chemotherapy

Dacarbazine was first approved by the US Food and Drug Administration in 1975, and despite never having demonstrated an OS benefit versus no treatment has served as the global 'reference therapy' used in randomized melanoma trials [76]. Dacarbazine is associated with a relatively modest response rate of ~5–15% and median duration of response of 1.5–4 months, and has not demonstrated a survival benefit versus best supportive care [20,77,78]. On the basis of recent trials in previously untreated, advanced melanoma, a median OS of ~9 months and a 1-year OS rate of ~36% represent the upper boundary of historical benchmarks for dacarbazine monotherapy [52,79–85].

Other cytotoxic compounds, including temozolomide, cisplatin and carboplatin, vinca alkaloids, taxanes, and nitrosoureas (e.g. fotemustine), have been investigated, but none have significantly improved outcomes compared with dacarbazine. Fotemustine has been approved by some European regulators and is often used in patients with melanoma metastatic to the brain because of its potential enhanced ability to cross the blood–brain barrier compared with dacarbazine [81,86]. Whether the addition of fotemustine to dacarbazine can delay the occurrence of brain metastases is unclear [85].

### Integration of approved, first-line agents into clinical practice

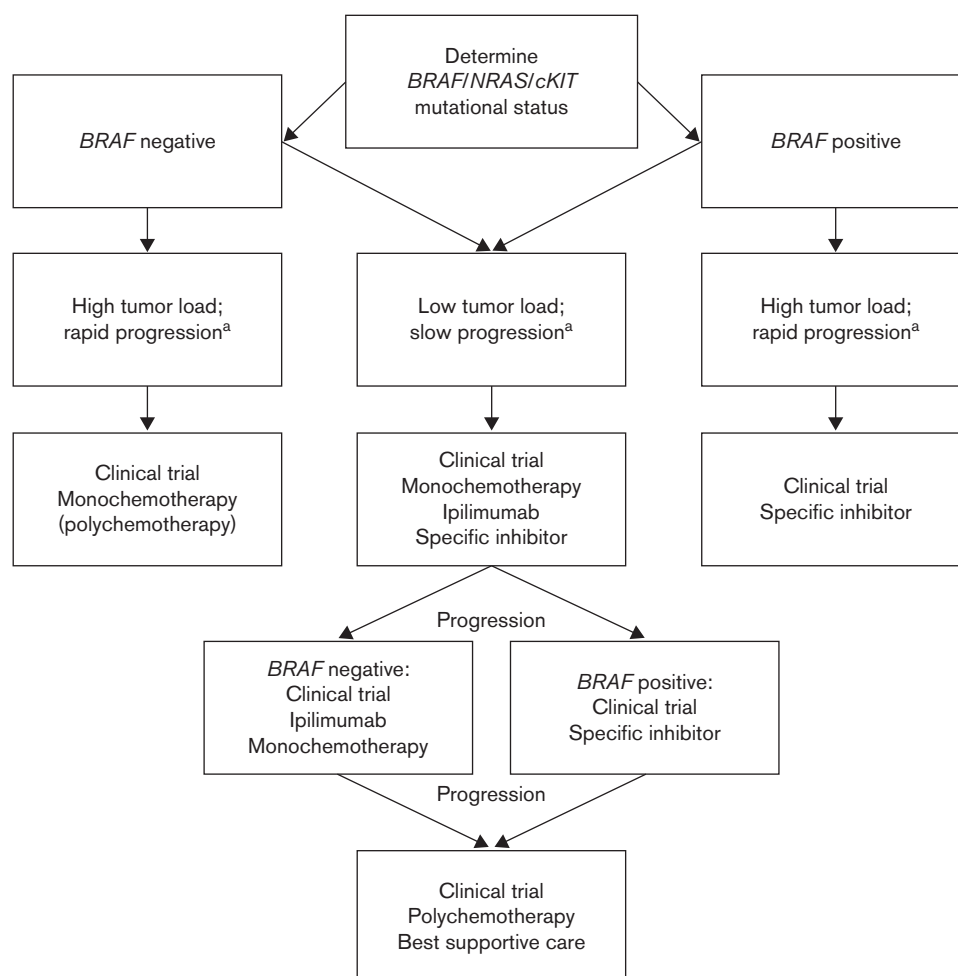
At present, when a patient with advanced melanoma attends a clinic for the first time, there are a number of treatment options to consider. As treatment decisions become increasingly complex, guidelines are becoming more pragmatic, considering the mechanism of action of the treatments, the individual patient and tumor characteristics, and the treatment goals (Fig. 1) [9]. While our discussion will focus on currently approved treatment options, it must not be forgotten that clinical trials should be considered for all patients with advanced melanoma, because a cure for all patients is still far away.

With more therapeutic options available for metastatic melanoma, it is important that treatment be tailored toward the individual. For example, patient characteristics, such as rate of progression and extent of tumor burden, should be considered when making treatment decisions. For patients with rapid tumor kinetics, a rapid reduction in symptoms is likely to be most important and buys time for potentially effective second-line treatments in parallel. If patients are symptomatic, a rapid reduction in tumor volume can translate into benefits in quality of life more or less immediately. By contrast, for patients with slowly progressing disease or a lower tumor burden, the goal of treatment should be long-term control of the disease. These differing goals will affect which treatment is the most suitable first-line option for individual patients. It is also important to note that, to date, no methodology for defining 'progression or disease kinetics' has been accepted.

Ipilimumab and selective BRAF inhibitors are replacing chemotherapy as first-line treatment options for patients with advanced melanoma. In addition, the German treatment guidelines pre-empted the EMA by suggesting that ipilimumab is an appropriate first-line treatment option for patients, irrespective of mutation status, although patients who survive long enough to receive the full course of treatment are likely to gain the most benefit (Fig. 1) [9]. For patients with a *BRAF* mutation who are unsuitable for treatment with ipilimumab (i.e. those who are symptomatic or have rapidly progressing disease), the choice is vemurafenib or dabrafenib. Currently, there is not enough guidance to choose between vemurafenib and dabrafenib. Disease kinetics, tumor burden, and, in *BRAF*-mutated patients specifically, the potential for post-treatment pattern of progression should also be considered [87,88]. Treating physicians currently have to make, at least in part, a 'gut decision'; however, the summary provided in Table 1 may help guide treatment choices.

The treatment of advanced melanoma has evolved rapidly over the past 5 years, and will continue to evolve, with new treatment approaches in advanced clinical development. Until data from randomized trials are

Fig. 1



Guidelines for the treatment of patients with advanced melanoma. <sup>a</sup>Life expectancy less than 12 weeks = rapidly progressing disease; more than 12 weeks = slowly progressing disease. Adapted with permission from Pflugfelder *et al.* [9].

Table 1 Summary of first-line treatment options available for use in Europe

Agents	Notes
Vemurafenib or dabrafenib	Associated with rapid responses, although duration of response is often limited because of the emergence of resistance; long-term benefit unknown [19–22,39] Unsuitable for patients with <i>BRAF</i> wild-type melanoma [12,13] Recommended for use in patients with <i>BRAF</i> V600-mutated metastatic melanoma who have bulky, symptomatic disease, high tumor load, and rapidly progressing disease [9,87] Vemurafenib has demonstrated activity in patients with symptomatic and asymptomatic brain metastases [32]; dabrafenib has demonstrated activity in patients with asymptomatic brain metastases [34]
Trametinib	Significantly improved PFS and OS when compared with chemotherapy in a phase 3 trial [42,43] Unsuitable for patients with <i>BRAF</i> wild-type melanomas Efficacy in subpopulations remains to be demonstrated (e.g. patients with brain metastases)
Ipilimumab	Unlike <i>BRAF</i> inhibitors, trametinib is not associated with the development of cutaneous squamous cell carcinomas [42,43] Can provide patients with durable tumor control and long-term survival benefits, although responses to treatment can be delayed [63,64,67] Recommended for use in patients with low tumor load and slowly progressing disease, regardless of mutational status; European guidelines recommend use in patients with life expectancy of 3–4 months who should be able to receive the full course of treatment [6,7,9,87] Demonstrated activity in patients with asymptomatic brain metastases [53]
Nivolumab	Demonstrated activity in elderly patients and patients with mucosal and uveal melanoma in a European EAP [89–91]
Pembrolizumab	Demonstrated survival benefit compared with dacarbazine in previously untreated melanoma without <i>BRAF</i> mutation [71]
Dacarbazine	Demonstrated survival benefit compared with ipilimumab in patients who were treatment-naïve or received one previous systemic therapy for advanced melanoma [72] Associated with a modest response rate; has never demonstrated a survival benefit [77,78] Suitable for <i>BRAF</i> wild-type patients who cannot be considered for ipilimumab or a clinical trial

cutSCC, cutaneous squamous cell carcinomas; EAP, Expanded Access Programme; OS, overall survival; PFS, progression-free survival.

available, recommendations based on the consensus of experts, such as the Society for Immunotherapy of Cancer, can provide guidance on optimal patient selection, sequencing of treatments, and ongoing patient monitoring [52]. Furthermore, fruitful collaboration between industry and healthcare professionals is needed if we are to continue to support high-quality patient care.

## Conclusion

The number of first-line options available for patients with advanced melanoma is increasing, and treatment decisions in melanoma are becoming ever more complex. Targeted therapies have demonstrated prolonged PFS and improved OS in patients with untreated *BRAF*-mutant melanoma; however, these agents are often associated with drug resistance, which can limit clinical benefit and affect outcomes. Patients may also benefit from treatment with ipilimumab, which can provide durable tumor control and long-term survival. The recent approvals of anti-PD-1 agents, as well as promising results from the combination of nivolumab and ipilimumab, will potentially offer more first-line options to clinicians to treat patients with advanced melanoma. The changing landscape underlines the importance of optimal treatment selection to maximize the best possible outcomes for patients with advanced melanoma.

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## Conflicts of interest

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